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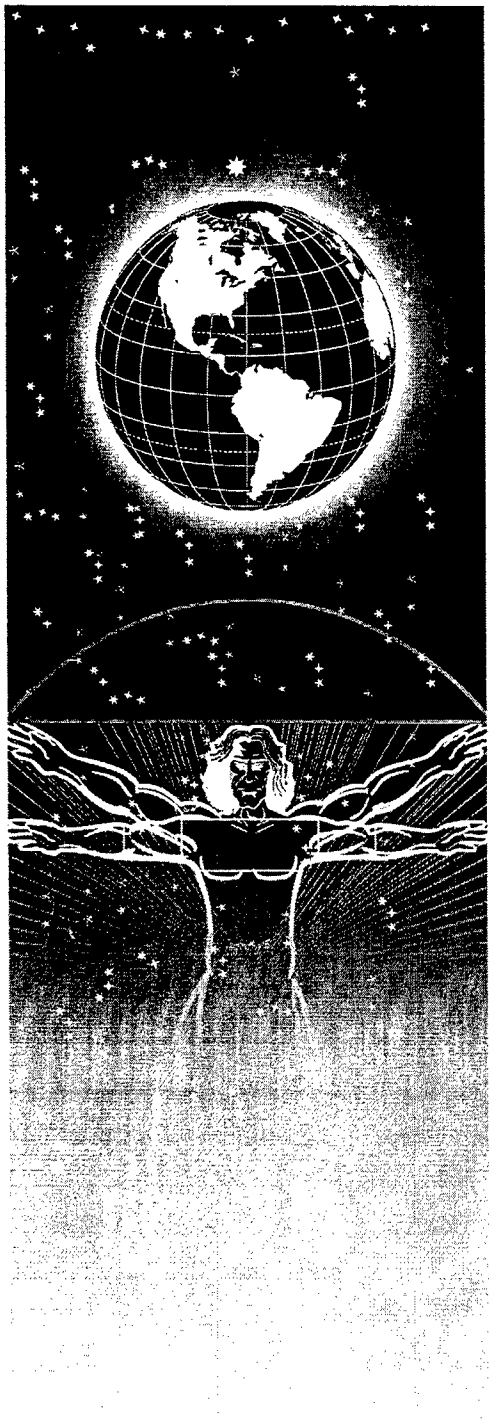

UNITED STATES AIR FORCE
RESEARCH LABORATORY

TOXICITY OF EXPERIMENTAL JET FUEL SYSTEM ICE-INHIBITING AGENTS: I. IN VITRO DOSIMETRY

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FOR THE DIRECTOR

Stephen R. Channel

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The potential toxicities of compounds to replace current US Air Force operational chemicals is of particular interest. A group of jet fuel system ice-inhibiting agent alternatives currently being evaluated for performance include derivatives of 1,3-dioxolane-4-methanols and 1,3-dioxanes. The experiments presented here were performed in support of Air Force Research Laboratory's Materials Directorate research on FSII alternatives. Our initial approach to evaluating potential toxicity utilized primary rat hepatocyte cultures for assessing acute toxicity. The experiments summarized here were performed to develop analytical methods for these chemicals and the assessment of potential variations in the aqueous concentrations of the test chemicals during cell culture experiments due to volatilization. The test chemicals were prepared at 1mM and 10mM concentrations and incubated in 6-well culture plates at 37 C for 0-6 hrs. Aliquots were taken at time intervals and analyzed by gas chromatography. These concentrations indicate the potential in vitro dosimetry for the cells in culture. The results indicate that for all but one (M-27) for M-DE and M-PE there was no significant change in chemical concentration of the chemicals tested, the aqueous concentrations do not vary substantially from their initial concentration over a six hour incubation.

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LIST OF ABBREVIATIONS

%	percent, grams per 100ml
°C	Degrees Celsius
DMSO	Dimethyl sulfoxide
FSII	Fuel system ice-inhibitor
GC/FID	Gas chromatography with flame ionization detector
h	Hour
HPLC	High Performance liquid chromatography
M	Molar, moles/liter
M-1	2,2-dimethyl-[1,3]-dioxolane-4-methanol
M-2	[1,3]-dioxolane-4-methanol
M-3	2-methyl-[1,3]-dioxolane-4-methanol
M-22	2-methyl-1,3-propanediol
M-26	2,2,5-trimethyl-[1,3]-dioxane
M-27	2,5-dimethyl-[1,3]-dioxane
M-DE	2-(2-methoxyethoxy)-ethanol
M-DP	Oxydipropanol
M-EG	Ethane-1,2-diol
M-EM	2-Methoxyethanol
M-G	Glycerol
M-PE	1-Ethoxy-2-propanol
min	Minute
mL	Milliliter
mM	Millimolar, millimoles/liter
MPDIOL	2-methyl-1,3-propanediol
uL	microliters, 0.000001 liter

PREFACE

This report is one of a series of interim technical reports describing the results of Task 2 of the Predictive Toxicology Program conducted at AFRL/HEST. The Predictive Toxicology Program is a collaborative effort that involves scientists from the Materials Directorate and Human Effectiveness Directorate of the Air Force Research Laboratory, in addition to outside academic scientists. Predictive Toxicology research (JON# 2312A202) is supported by the Air Force Office of Scientific Research (AFOSR), under the direction of Dr. Walt Kozumbo (AFOSR). This report describes experiments concerning the application of *in vitro* toxicology methods for the assessment of fuel system ice inhibitor toxicity. The research described in this report began October 1997 and was completed in April 1999 under U.S. Air Force Contract No. F41624-96-C-9010 (ManTech/Geo-Centers Joint Venture). Maj. Stephen R. Channel serves currently as Contract Technical Monitor for the U.S. Air Force, Air Force Research Laboratory, Operational Toxicology Branch.

I. INTRODUCTION

The US Air Force and other DoD agencies have pursued the potential replacement of current operational chemicals with alternatives that pose less potential toxic risk. One area of interest is in fuel system ice inhibitors (FSIIs) [1]. Alternatives to glycol ethers, such as diethylene glycol monomethyl ether (M-DE), are being investigated. In addition, new FSIIs are being synthesized through Research and Development (R+D) activities of the Materials Laboratory. Three derivatives of 1,3-dioxolane-4-methanol (M-1, M-2, and M-3) and two derivatives of 1,3-dioxane (M-26 and M-27) are evaluated in this report. In addition, M-DE and a number of other chemicals are being evaluated as reference compounds.

The development of fuel system ice inhibitors is an example of an integrated approach to designing new operational compounds that are potentially the least toxic, while exhibiting acceptable performance characteristics [2]. This project involves our toxicology lab, as well as scientists from the Materials Directorate of the Air Force Research Laboratory. When undertaking the selection of chemicals that are to be developed and pursued, current DoD acquisition strategies take into consideration the potential toxicities associated with human exposure to those chemicals of interest [3,4]. The utilization of various *in vitro* testing approaches is intended to assist our ability to address the question of potential chemical toxicity in a strategic and timely fashion. Our initial approach to evaluating the potential toxicities of these chemicals includes the assessment of acute toxicity in primary rat hepatocyte cultures.

Dosimetry is a concern in toxicology, both *in vivo* and *in vitro*. Monitoring of blood, tissue, or media concentrations is performed routinely to determine the levels of test chemical that are potentially available to the target tissue, cell, or molecule. Solubility, phase partitioning, and volatility are some of the factors affecting the bioavailability of a chemical.

In order to address the potential role of volatility on *in vitro* dosimetry, experiments were performed to develop analytical methods for the detection and quantification of these chemicals and to assess the potential variations in aqueous concentrations of the test chemicals during cell culture experiments, due to volatilization. Potential volatilization of the test article is a concern for the *in vitro* testing of these FSIIs. The rate of loss of a chemical from the aqueous phase into the gas phase is a function of the concentration gradient, the concentration decrease from the aqueous phase would follow a pattern of exponential decay [5]. Thus, although *in vitro* exposures are often conducted for periods greater than 12 hours, the greatest change in concentration would have occurred before 6 hours. This means that an initial assessment out to 6 hours would provide sufficient insight into whether the change in chemical concentration would be substantial.

Here, we chose concentrations of 1 and 10 millimolar (mM) for these experiments, because those concentrations are at the upper end of the doses used in our standard *in vitro* testing design. These doses are sufficient to elicit biological response *in vitro* [3,4]. The dosimetry experiments were conducted at 37°C, since that is the temperature at which the cells in media would be exposed and incubated with these chemicals. The samples were prepared in water, instead of media, to reduce confounding factors, such as macromolecular binding that may occur with some media. Concentrations were determined by comparison to standard curves developed for each chemical. Method development for the gas chromatography analysis with flame ionization detection (GC/FID) method was performed for each chemical.

II. MATERIALS AND METHODS

Chemicals

Dr. George Mushrush (George Mason University, Fairfax, VA) provided all of the test chemicals used in dosing solutions. All chemicals were stored at room temperature until experimental analysis. Chemical structures and physical/chemical properties are shown in Table 1.

Analytical Methods

Chemical test solutions (M-1, M-2, M-3, M-22, M-26, M-DE, M-DP, M-EG, M-EM, M-G, M-PE) were prepared in nanopurified distilled water. Solutions of the test chemical M-27 was prepared in 10% DMSO in H_2O. For the low dose range standard curves, solutions of each chemical were prepared in 5 concentrations (0, 0.25, 0.5, 0.75, 1.0mM). For the high dose range standard curves, solutions of each chemical were prepared in 5 concentrations (0, 2.5, 5.0, 7.5, 10.0 mM). Aqueous solutions of the test chemicals were analyzed by gas chromatography (GC). Samples (0.2µl) were injected by autosampler onto a 0.53mm X 30m SPB-1 column (Supelco, Bellefont, PA) in a Varian 3700 (Palo Alto, CA) gas chromatograph (GC) with a flame ionization detector (FID). Carrier gas flow was 4 mL/min helium. Make-up gas flow was 23 mL/min helium. The column oven temperature program was adjusted for each test chemical (See Table 2).

TABLE 1. Test Chemicals

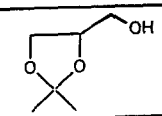
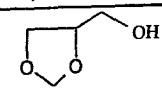
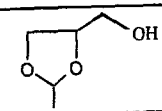
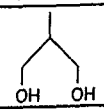
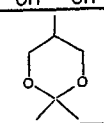
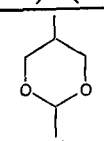
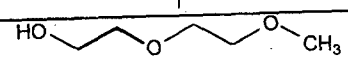
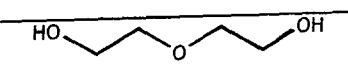
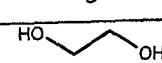
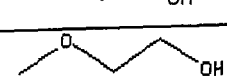
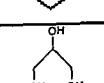
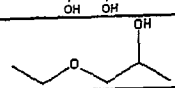
M-#	IUPAC Name (Synonyms)	Molecular Structure	CAS#	Molecular Formula	Formula Weight	Relative Density (g/ml) @20°C	Boiling Point (°C) @1atm	Vapor Pressure (mmHg) @37°C	LogP (est.)
M-1	2,2-dimethyl-[1,3]-dioxolane-4-methanol (SOLKETAL)		100-79-8	$C_6H_{12}O_3$	132.16	1.063	182.0	0.5	1.07
M-2	[1,3]-dioxolane-4-methanol (Glycerol formal)		5464-28-8	$C_4H_8O_3$	104.11	1.215	193.0	0.4	-0.60
M-3	2-methyl-[1,3]-dioxolane-4-methanol		3773-93-1	$C_5H_{10}O_3$	118.13	1.12	187.0	0.5	-0.17
M-22	2-methyl-1,3-propanediol (MPDIOL Glycol)		2163-42-0	$C_4H_{10}O_2$	90.12	1.02	213.0	0.07	-0.92
M-26	2,2,5-trimethyl-[1,3]-dioxane		25796-25-2	$C_7H_{14}O_2$	130.19	0.999	71.0	20.0	1.27
M-27	2,5-dimethyl-[1,3]-dioxane		20615-12-7	$C_6H_{12}O_2$	116.16	0.964	125.5	39.0	0.53
M-DE	2-(2-methoxyethoxy)-ethanol (Diethylene glycol mono-methyl ether; DIEGME)		111-77-3	$C_5H_{12}O_3$	120.15	1.025	193.0	1.0	-1.18
M-DP	Oxydipropanol (Dipropylene glycol)		25265-71-8	$C_6H_{14}O_3$	134.18	1.025	229.0	0.1	-1.30
M-EG	Ethane-1,2-diol (Ethylene glycol)		107-21-1	$C_2H_6O_2$	62.08	1.11	198.0	0.06	-1.37
M-EM	2-methoxyethanol (EGME)		109-86-4	$C_3H_8O_2$	76.1	0.975	124.0	18.0	-0.75
M-G	Glycerol		56-81-5	$C_3H_8O_3$	92.09	1.26	290.0	0.001	-1.99
M-PE	1-ethoxy-2-propanol		1569-02-4	$C_5H_{12}O_2$	104.13	0.896	132	10.0	0.15

TABLE 2. Gas Chromatograph Column Oven Temperature Programs

Chemical	Program
M-1	60°C increased 5°C/min to 100°C
M-2	58°C isothermal
M-3	70°C isothermal
M-22	95°C increased 1°C/min to 103°C
M-26	35°C increased 1°C/min to 75°C
M-27	45°C isothermal Post run DMSO bake-off - raise 15°C/min to 160°C, hold 5 min.
M-DE	75°C increased 1°C/min to 85°C
M-DP	85°C increased 1°C/min to 95°C
M-EG	35°C increased 1°C/min to 75°C
M-EM	75°C increased 1°C/min to 83°C
M-G	95°C increased 1°C/min to 103°C
M-PE	35°C isothermal

The injector and detector temperatures were 200°C and 240°C, respectively. Chemical samples and standards in water (except in the case of M-27, which also included 10% DMSO) were analyzed in the same manner. The results were processed with Perkin-Elmer Nelson integration software (Norwalk, CT). Sample concentrations were determined by measurement of peak areas, then calculated based on the standard curve results.

Experimental Approach

For the dosimetry experiment, solutions were prepared for each of the FSII chemicals in two concentrations, 1mM and 10mM. Compounds M-26 and M-EG were not tested for dosimetry. One mL of each chemical, either the 1mM or 10mM concentration, was added to each well of a 6-well culture plate.

Three plates were prepared for each chemical and concentration. The plates were covered and placed in an incubator at 37°C for 6 hours. During the incubation, approximately 1ml of the test solution was removed from a single well from each of three plates at specific time points (0, 1, 2, 4, 6h).

Data Analysis

The means of the peak areas from the three injections were used when analyzing the results of the GC analysis. The results of the standard curves were analyzed using Excel (Microsoft Corp, Palo Alto, CA). Chemical concentrations in the dosimetry experiments were calculated based on the standard curves for each chemical. The natural logs of the means of the three results for each time point were used for linear regression analysis to determine whether the changes in chemical concentration were significant ($p<0.05$) using SigmaStat software (Jandel Scientific, San Rafael, CA). Changes in concentration greater than 10% after 6 hours were considered relevant to potential *in vitro* dosimetry, where metabolism is not a factor in the kinetics of the loss of the chemical.

III. RESULTS AND DISCUSSION

Method Validation

Figures 1, 3, 5, 7, 9, 11, 13, 15, 16, 17, and 18 show chromatograms from the GC/FID analysis of the test chemicals. Since the chemicals were not recently synthesized, and quality control for chemical synthesis was not controlled by our laboratory, the purity of some of the chemicals was suspect from the outset. For some chemicals, the GC/FID analysis revealed single major species; for others, there were apparent breakdown or synthesis by-products present. The peaks were later verified by GC with mass spectrometry detection (data not shown). For those with single major peaks, M-1, M-22, M-27, M-DE, and M-PE (Figs. 1, 5, 7, 9, 13), the peak areas for the major peaks was used for estimating the chemical concentration. For M-2 (Fig. 3), the four major peaks were used for concentration estimation. For M-DP (Fig. 11), the two major identified peaks were used.

Methods for GC/FID analysis of compounds M-3 (Fig. 15), M-26 (Fig. 16) and M-EG (Fig. 17), M-EM (Fig. 18), and M-G (Fig. 19) were developed. However, these chemicals were not used in the dosimetry experiment. M-3, M-EM, and M-G gave insufficient separation by GC analysis.

Figures 2, 4, 6, 8, 10, and 12 show the corresponding standard curves for the FSIIs in the low dose range (0, 0.25, 0.5, 0.75, 1.0mM) and the high dose range (0, 2.5, 5.0, 7.5, 10.0 mM) and analyzed by GC/FID. The resulting standard curves show the efficacy of our approach to quantifying the species of interest. These standard curves were used for calculating the chemical concentrations for the dosimetry experiments.

Figure 1. M-1 GC/FID Chromatogram

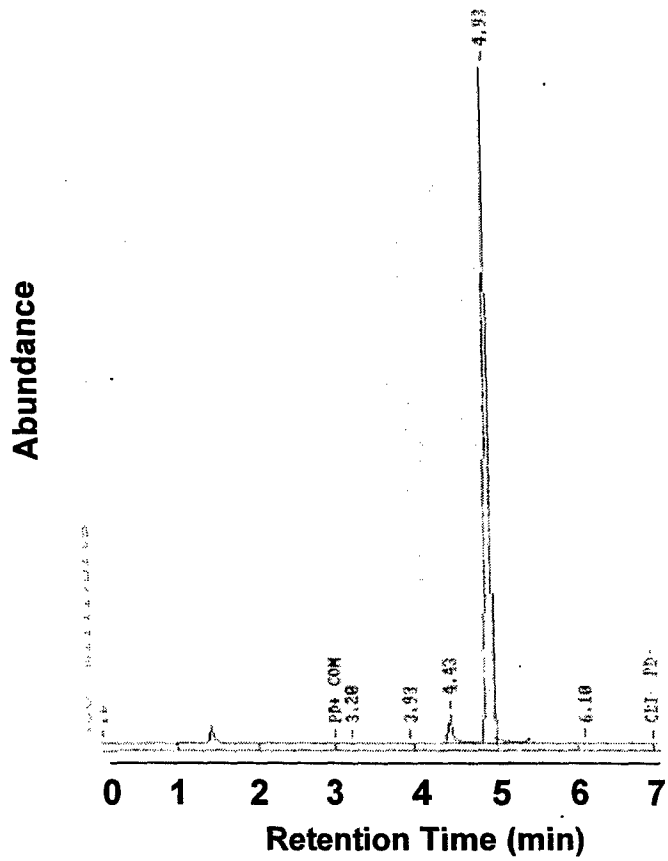
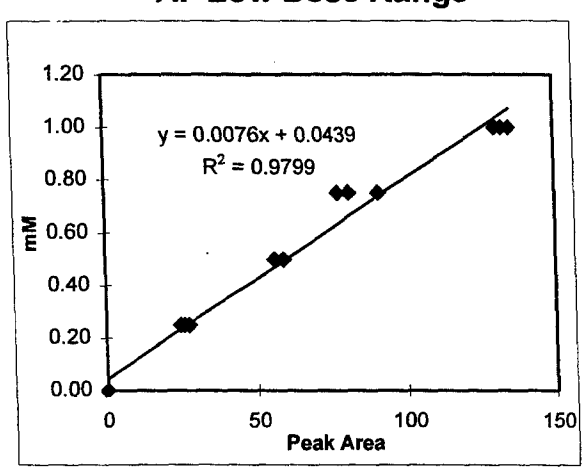


Figure 2. M-1 Concentration Standard Curves

A. Low Dose Range



B. High Dose Range

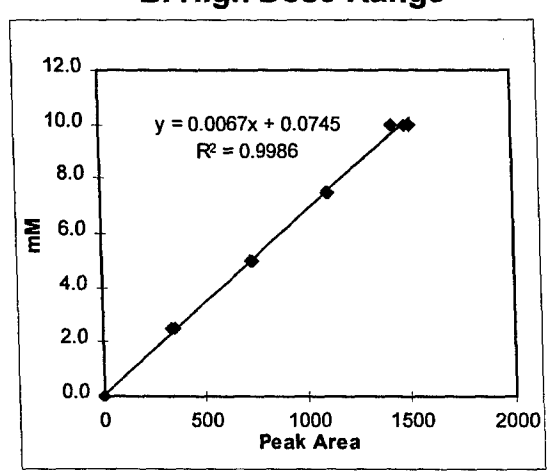


Figure 3. M-2 GC/FID Chromatogram

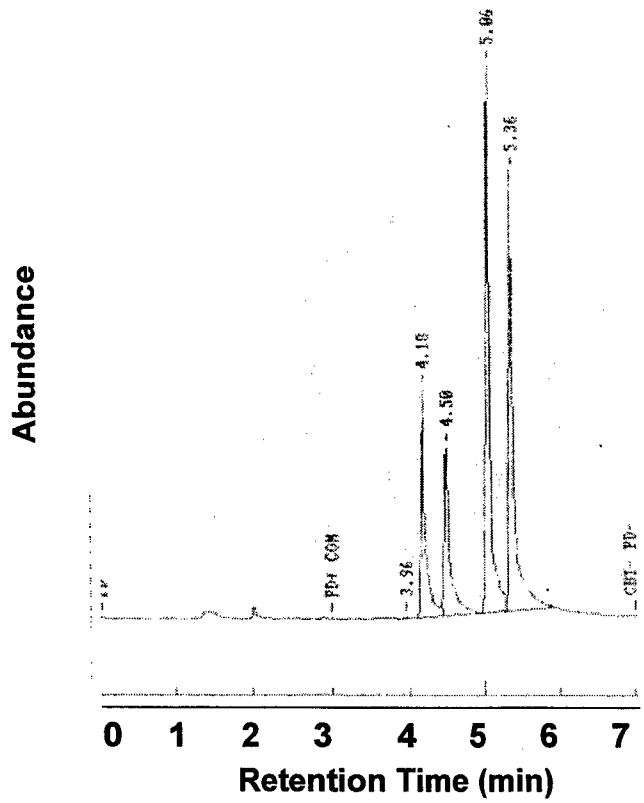
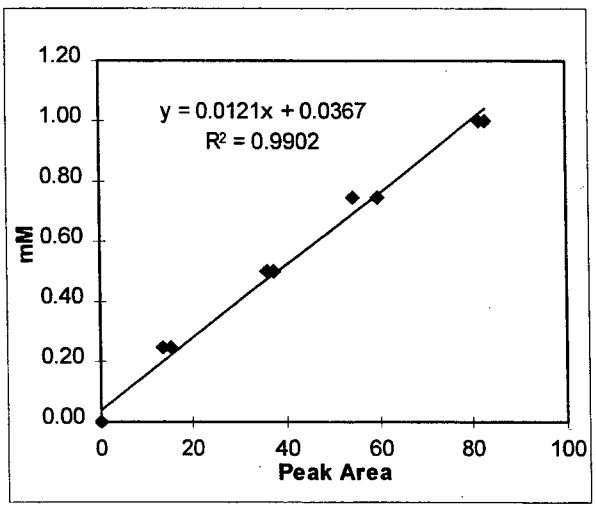


Figure 4. M-2 Concentration Standard Curves

A. Low Dose Range



B. High Dose Range

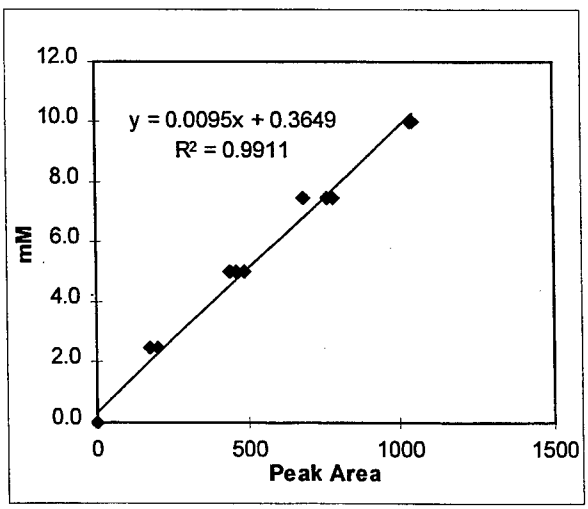


Figure 5. M-22 GC/FID Chromatogram

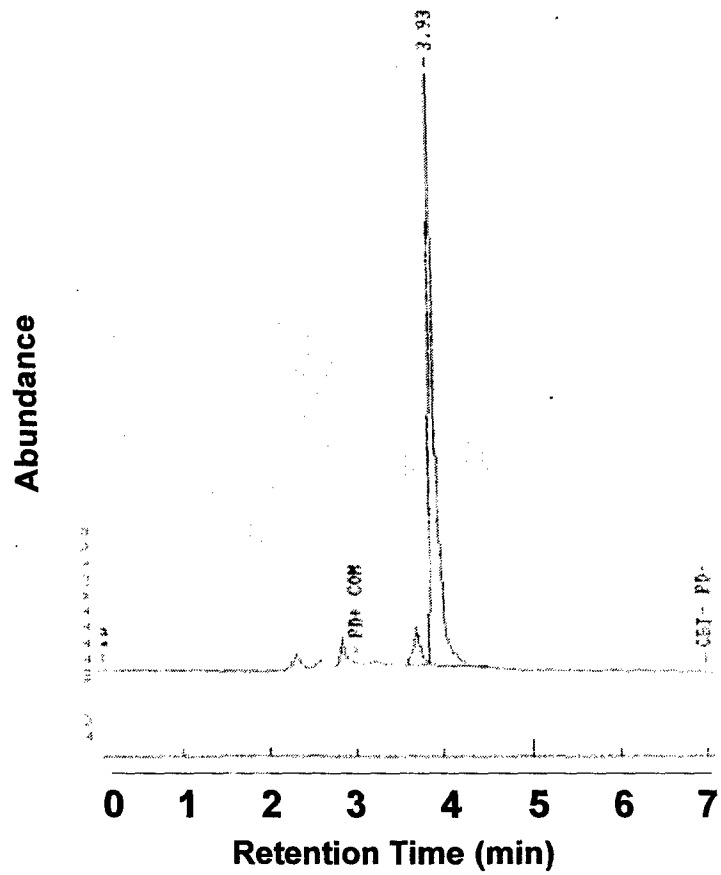
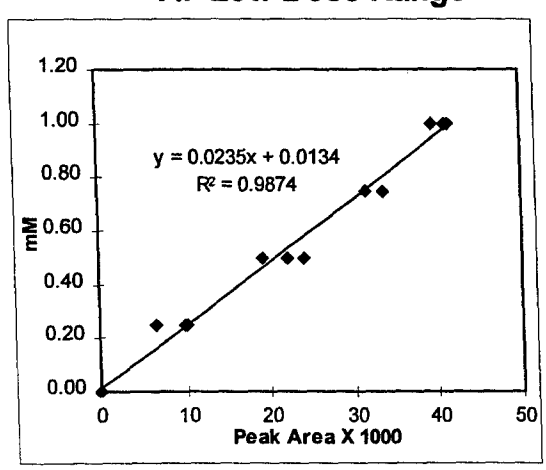


Figure 6. M-22 Concentration Standard Curves

A. Low Dose Range



B. High Dose Range

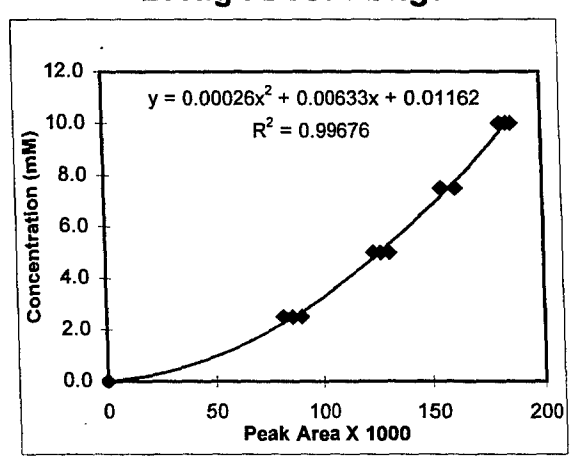


Figure 7. M-27 GC/FID Chromatogram

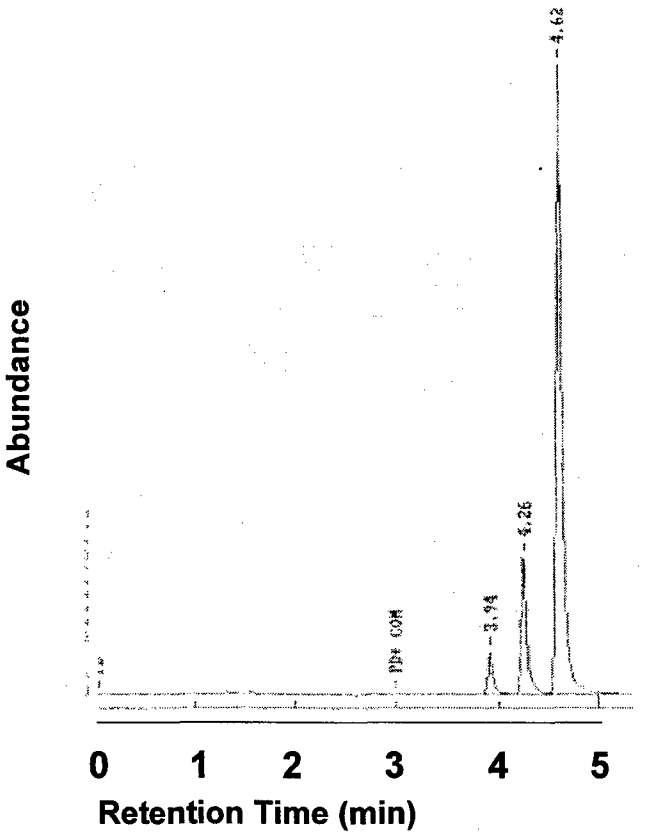
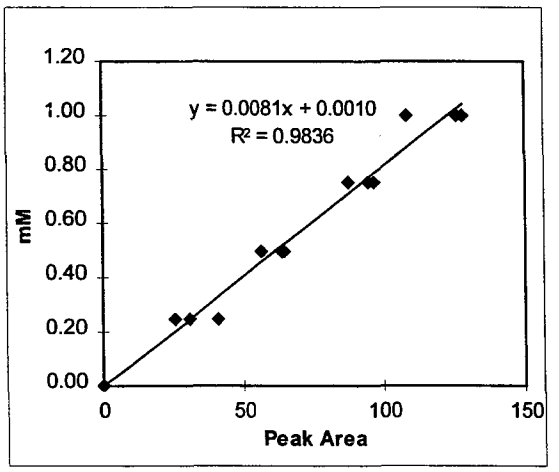


Figure 8. M-27 Concentration Standard Curves

A. Low Dose Range



B. High Dose Range

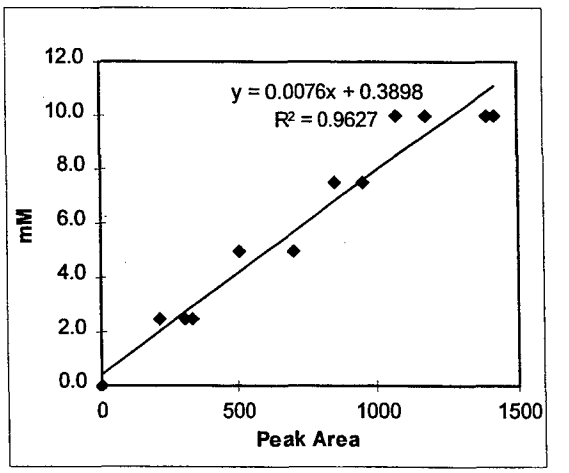


Figure 9. M-DE GC/FID Chromatogram

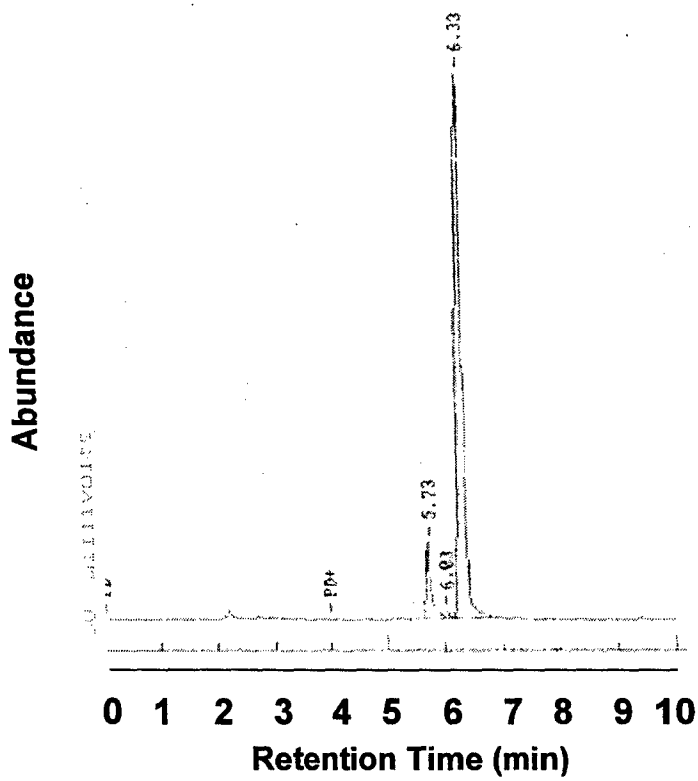
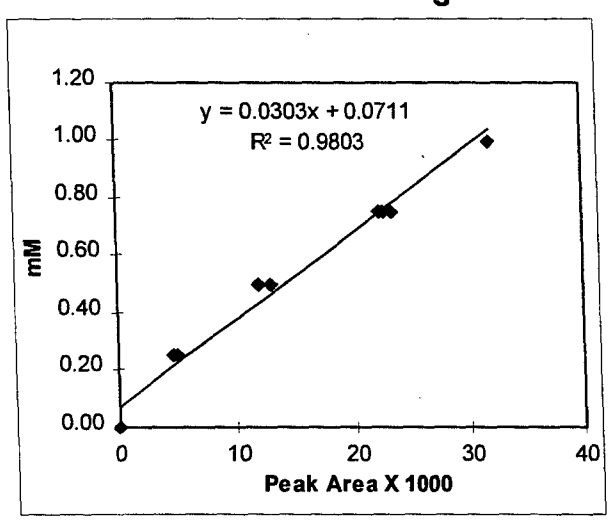


Figure 10. M-DE Concentration Standard Curves

A. Low Dose Range



B. High Dose Range

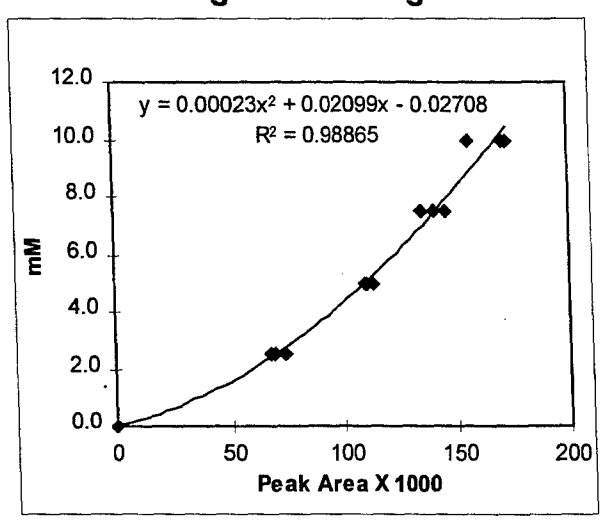


Figure 11. M-DP GC/FID Chromatogram

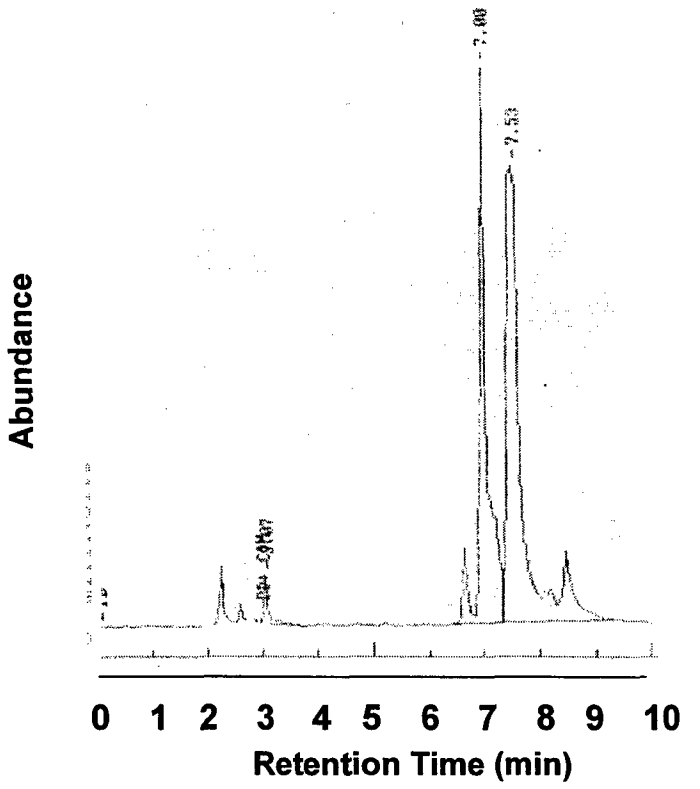
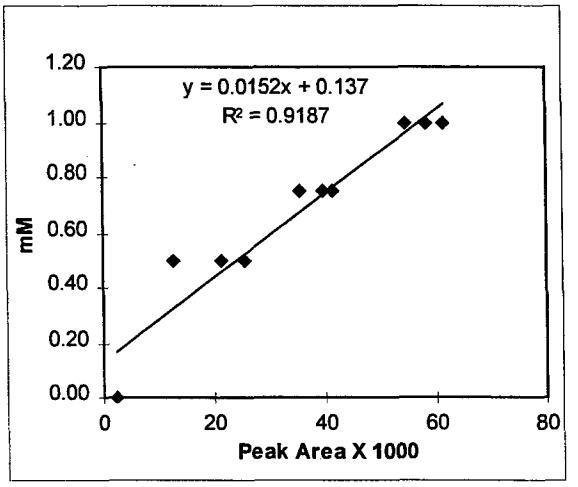


Figure 12. M-DP Concentration Standard Curves

A. Low Dose Range



B. High Dose Range

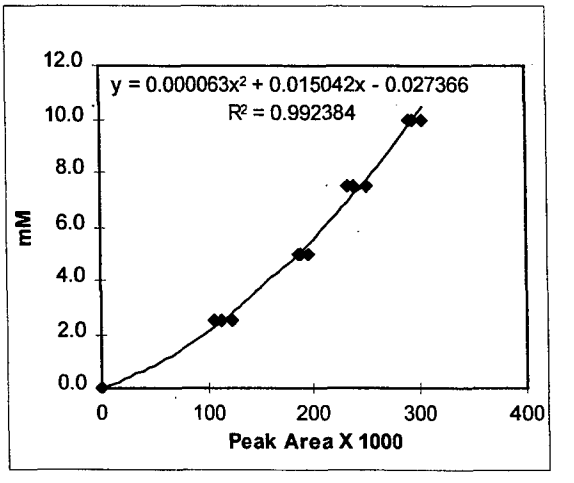


Figure 13. M-PE GC/FID Chromatogram

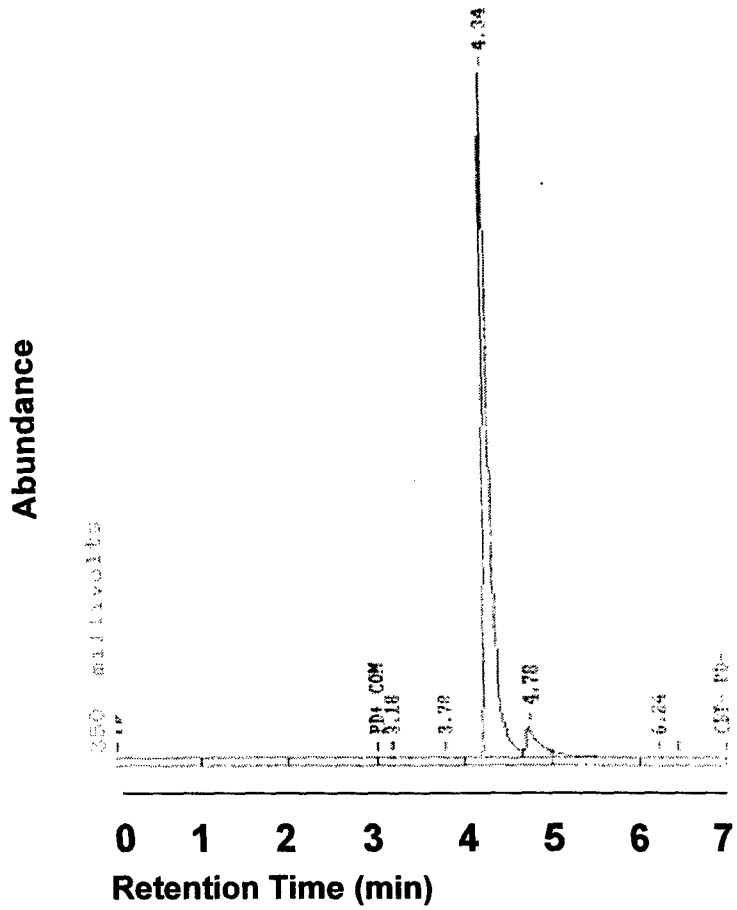
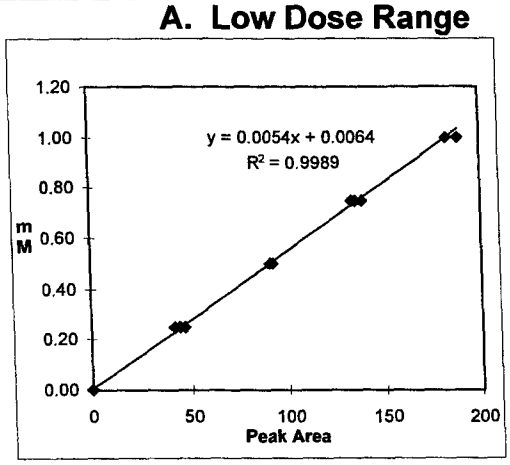


Figure 14. M-PE Standard Curves

A. Low Dose Range



B. High Dose Range

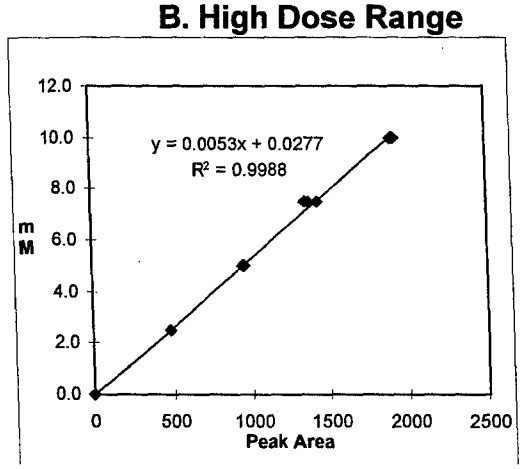


Figure 15. M-3 GC/FID Chromatogram

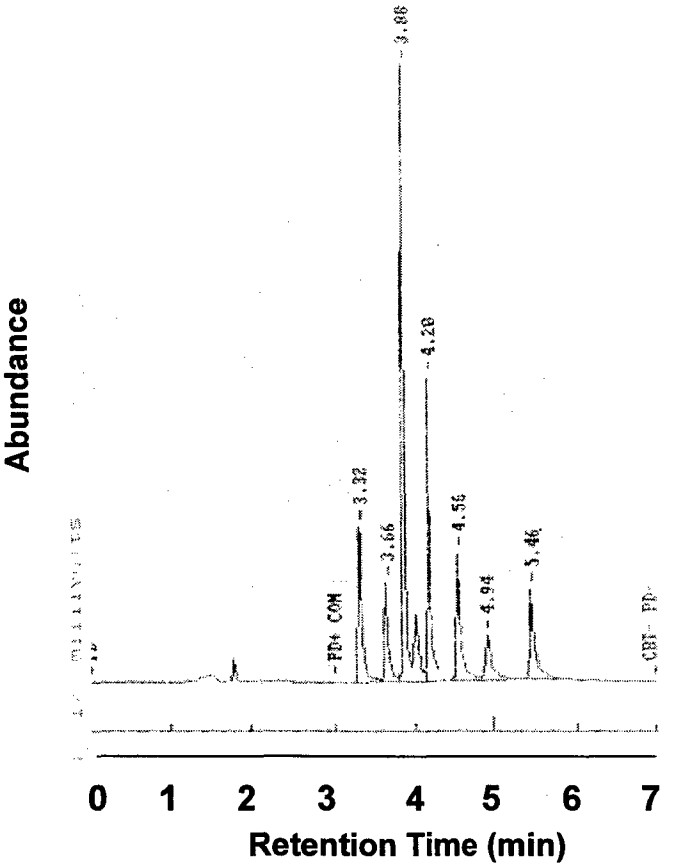


Figure 16. M-26 GC/FID Chromatogram

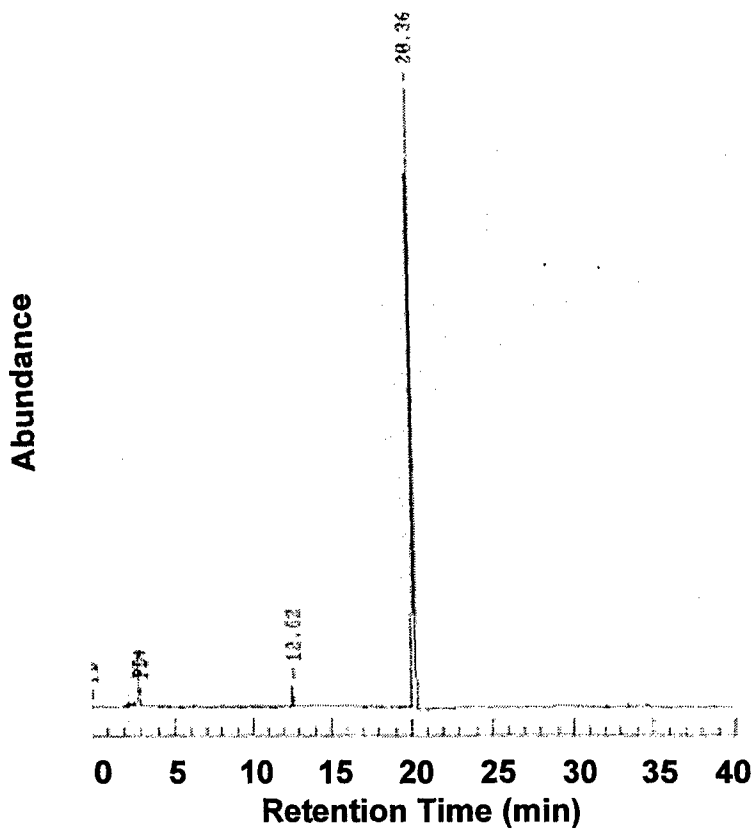


Figure 17. M-EG GC/FID Chromatogram

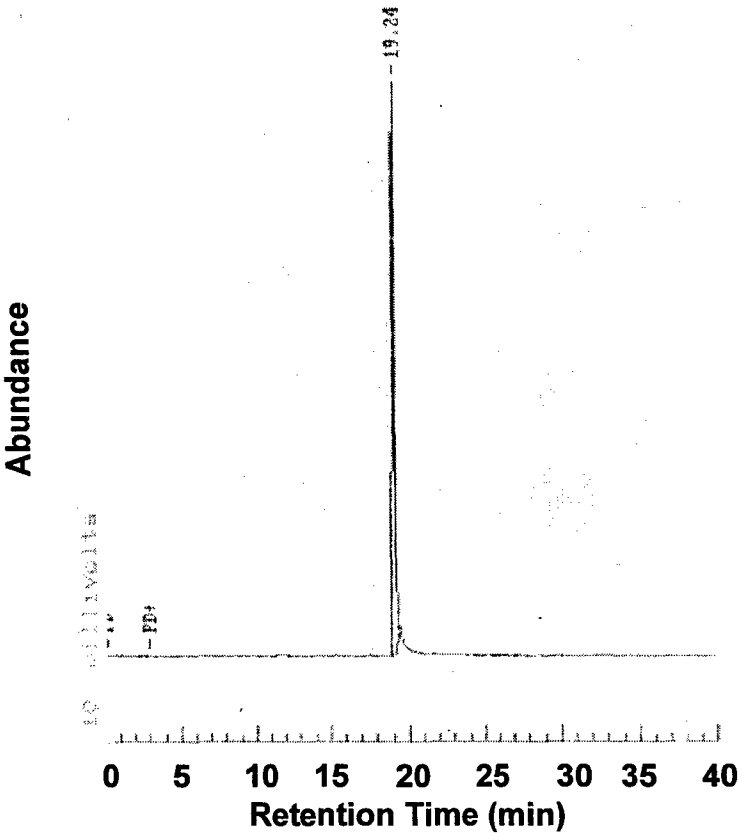


Figure 18. M-EM GC/FID Chromatogram

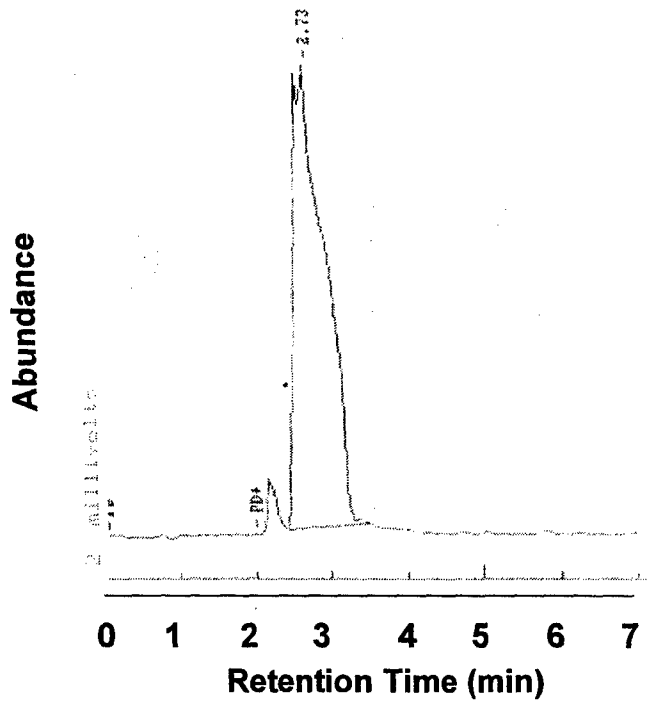
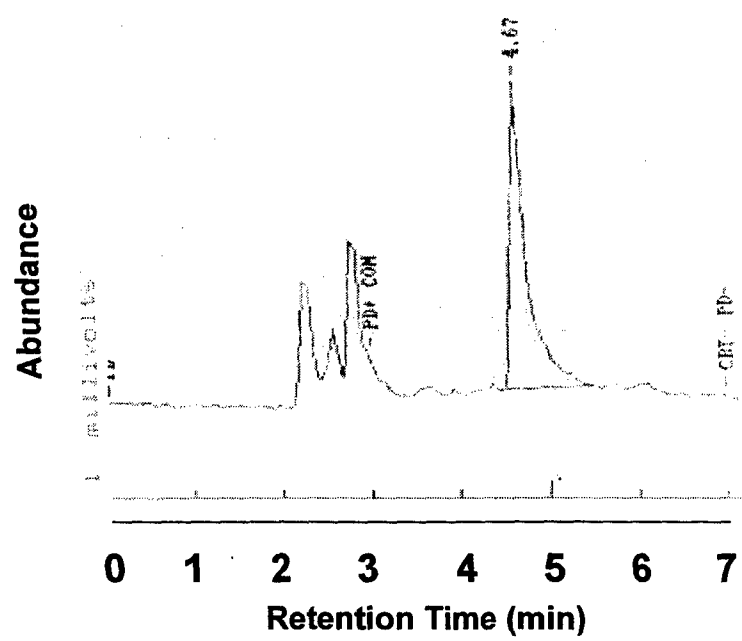


Figure 19. M-G GC/FID Chromatogram



In vitro Dosimetry

Figures 20-26 show the results of the GC/FID analysis of the individual test chemicals at the two concentrations (1 and 10mM) over time. The criteria for a concentration change to be relevant to *in vitro* dosimetry were that the change must be a statistically significant trend (as determined by regression analysis) that resulted in a concentration +/-10% of a given chemical's concentration at 0hr.

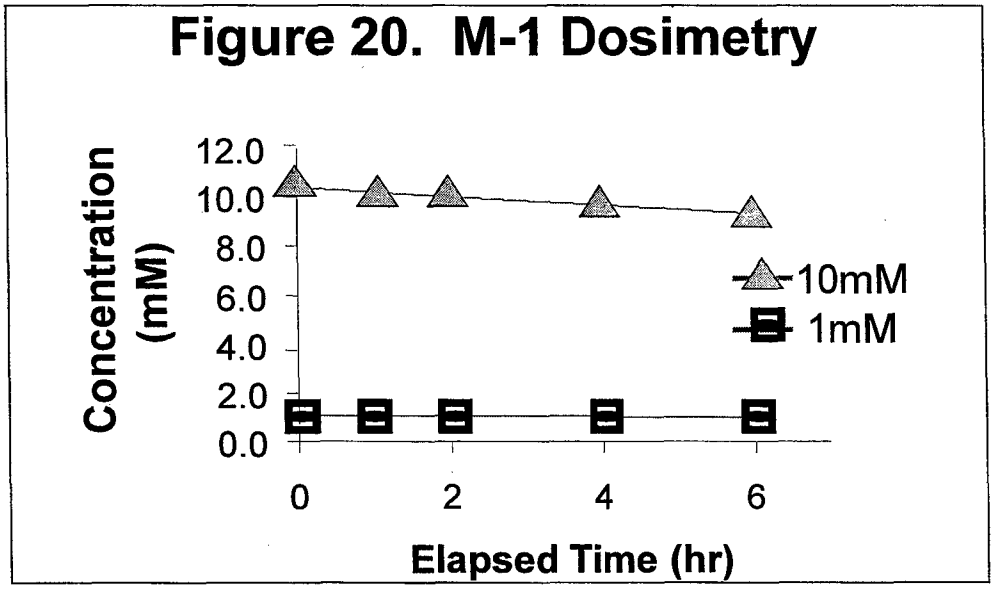


Figure 21. M-2 Dosimetry

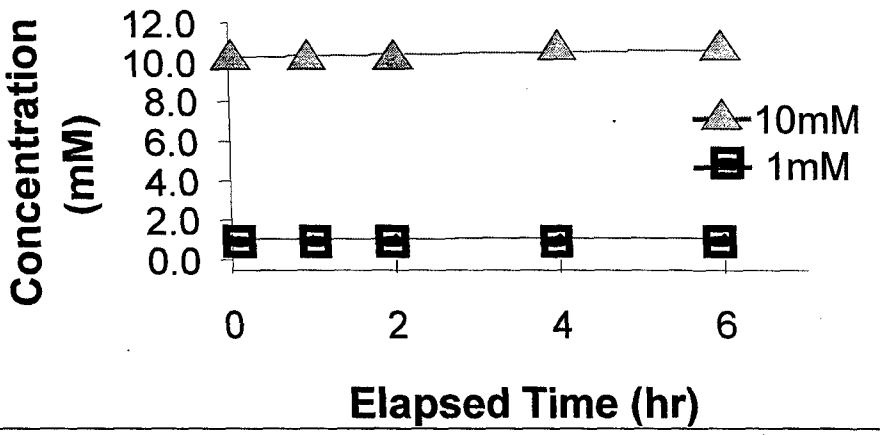
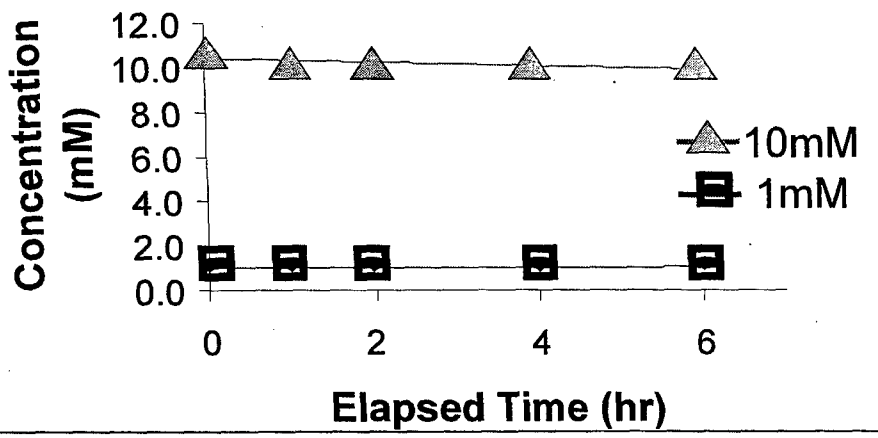
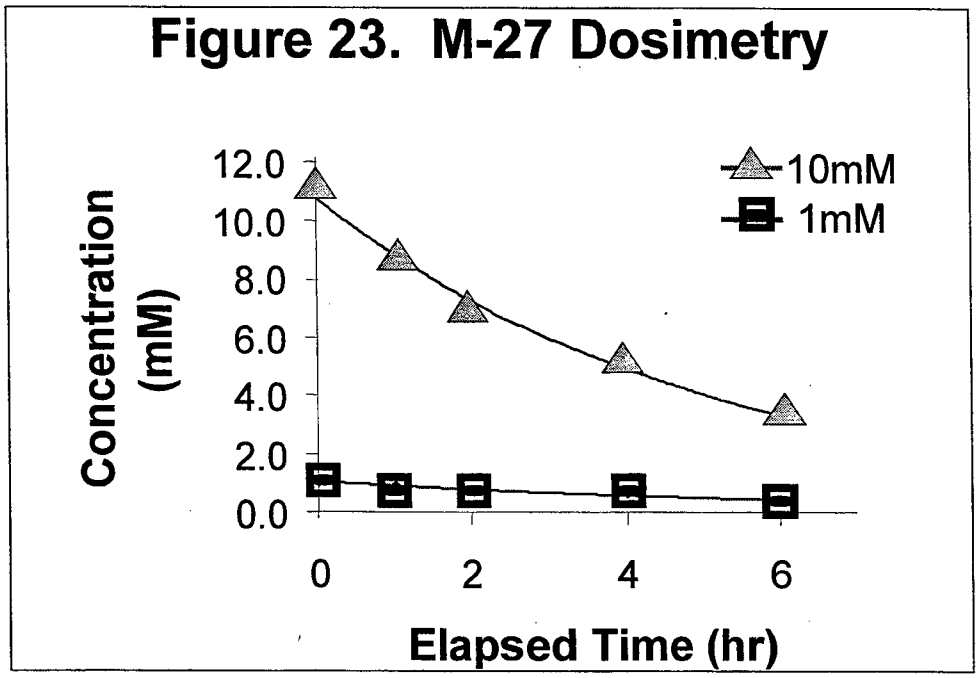


Figure 22. M-22 Dosimetry



Changes in chemical concentration were statistically significant ($p<0.05$, $r^2>0.6$) for M-1 at 10mM (Fig. 23), and M-22 at 1mM (Fig. 26). However, after 6 hours the net changes in the concentrations of the M-1 and M-22 compounds were less than ten percent (10%) of the initial concentrations (at t_0). These changes were not considered biologically relevant to experimental testing conditions, since a change less than 10% after 6 hours corresponds to a $t_{1/2}$ for the chemical in solution that would be greater than 40 hours.



The changes in concentration for M-27 at both 1 and 10mM (Fig. 23) were significant and relevant. At 1mM, after 6 hours, the concentration decreased 60%, corresponding to a $t_{1/2}$ of 4.5h ($p<0.05$, $r^2=0.90$). For 10mM, after 6 hours, the concentration had decreased 70%, corresponding to a $t_{1/2}$ of approximately 3.5h ($p<0.05$, $r^2=0.962$). These changes in M-27 over this time period are a potential concern for *in vitro* testing of this chemical.

A modification in dosing regimen should be considered when assessing the toxicity of M-27 with dosing periods greater than a few hours. Without such modifications, the toxicity of M-27 may be underestimated by certain *in vitro* testing systems. For M-2, M-DE, M-DP and M-PE there were no significant changes in chemical concentrations.

Figure 24. M-DE Dosimetry

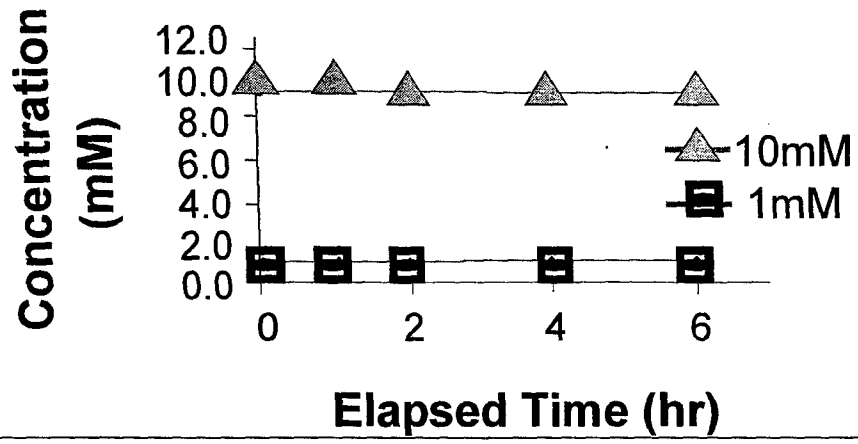
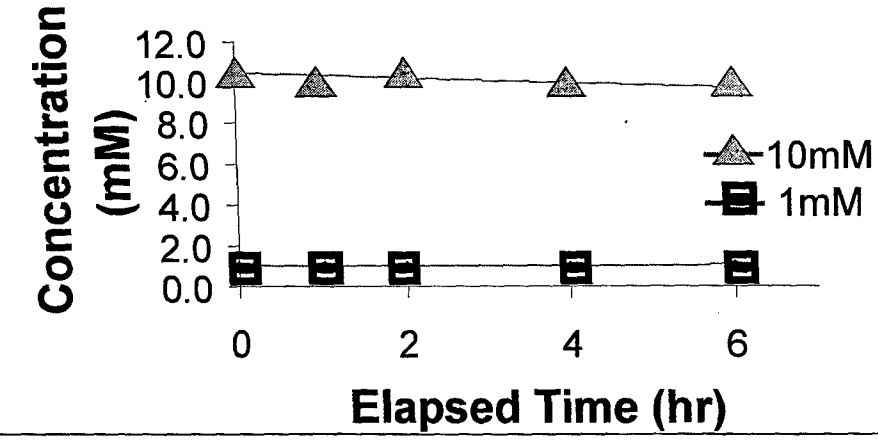


Figure 25. M-DP Dosimetry



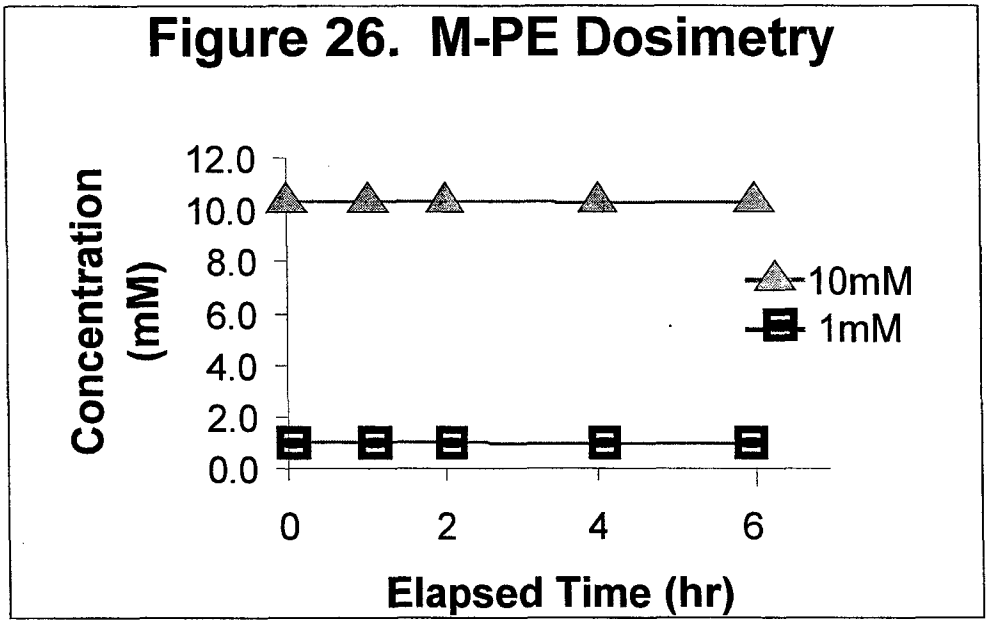


Figure 26. M-PE Dosimetry
Concentration (mM)
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0
2
4
6
Elapsed Time (hr)
10mM
1mM

IV. SUMMARY

- All 12 test chemicals were analyzed by GC/FID. Some chemicals were of insufficient purity to yield suitable GC analysis.

- The results of the dosimetry experiment for 10 test chemicals confirm that the initial target concentrations were achieved in the aqueous solutions for all FSII's of interest.

- The results of the time-course analysis of the test chemicals show that there is little concern for loss of these test articles from aqueous solution during the 6 hour time period used in this experiment, except for compound M-27.

- For those chemicals that exhibited virtually no change (M-1, M-2, M-22, M-DE, M-DP, M-PE) it is not likely that an effect on dosimetry would occur in an *in vitro* experiment simply due to loss of the test chemical by volatilization during the time period assessed here. However, testing by the method presented here does not consider potential metabolism that may occur in actual cell culture systems.

V. REFERENCES

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3. Geiss, KT; Channel, SR; and Frazier, JM. 1998. Comparative molecular toxicities of glycol-based ice-inhibiting agents. *The Toxicologist* 42:315.

4. Geiss, KT; Bachowski, S; Frazier, JM. 1998. Potential role of oxidative stress in the *in vitro* toxicity of 1,3-dioxolane derivatives. *Free Radical Biology and Medicine* 25(Supp 1):S22.

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